

What is claimed is:

- 1 1. A method for identifying an OP-1 receptor-binding analog, said
2 analog being characterized as having substantially the same
3 binding affinity for a cell surface receptor as OP-1, the method
4 comprising the steps of:
 - 5 (a) providing a sample containing a protein selected from the group
6 consisting of:
 - 7 (i) a polypeptide chain comprising an amino acid sequence
8 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an
9 OP1-binding analog thereof;
 - 10 (ii) a polypeptide chain comprising an amino acid sequence
11 defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an
12 OP1-binding analog thereof;
 - 13 (iii) a polypeptide chain comprising an amino acid sequence
14 defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an
15 OP1 binding analog thereof;
 - 16 (iv) a polypeptide chain having binding affinity for OP-1 and
17 sharing at least 40% amino acid identity with residues 23-
18 122 of Seq. ID No. 7 (ALK-6),;
 - 19 (v) a polypeptide chain having binding affinity for OP-1 and
20 encoded by a nucleic acid obtainable by amplification with
21 one or more primer sequences defined by Seq. ID Nos. 12-15;
22 or
 - 23 (vi) a polypeptide chain having binding affinity for OP-1 and
24 encoded by a nucleic acid that hybridizes under stringent
25 conditions with a nucleic acid comprising the sequence
26 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;
 - 27 (b) contacting said sample with a candidate OP1 receptor- binding
28 analog; and
 - 29 (c) detecting specific binding between said candidate OP1 receptor-
30 binding analog and said protein.
- 1 2. A method for identifying an OP-1 receptor-binding analog, said
2 analog being characterized as having substantially the same
3 binding affinity for a cell surface receptor as OP1, the method
4 comprising the steps of:

- 5 (a) providing a cell that expresses a surface receptor protein having
6 binding specificity for OP-1 selected from the group consisting
7 of:
8 (i) a polypeptide chain comprising an amino acid sequence
9 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an
10 OP1-binding analog thereof;
11 (ii) a polypeptide chain comprising an amino acid sequence
12 defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an
13 OP1-binding analog thereof;
14 (iii) a polypeptide chain comprising an amino acid sequence
15 defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an
16 OP1 binding analog thereof;
17 (iv) a polypeptide chain having binding affinity for OP-1 and
18 sharing at least 40% amino acid identity with residues 23-
19 122 of Seq. ID No. 7 (ALK-6),;
20 (v) a polypeptide chain having binding affinity for OP-1 and
21 encoded by a nucleic acid obtainable by amplification with
22 one or more primer sequences defined by Seq. ID Nos. 12-15;
23 or
24 (vi) a polypeptide chain having binding affinity for OP-1 and
25 encoded by a nucleic acid that hybridizes under stringent
26 conditions with a nucleic acid comprising the sequence
27 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;
28 (b) contacting said cell with a candidate OP1 receptor-binding
29 analog; and
30 (c) detecting induction of an OP-1-mediated cellular response.
- 1 3. The method of claim 2 wherein said OP-1 mediated cellular response
2 detected in step (c) is induction of a kinase activity, inhibition of
3 epithelial cell growth, or induction of a cell differentiation
4 marker.
- 1 4. The method of claim 2 or 3 wherein said cell comprises a transfected
2 nucleic acid comprising a reporter gene in operative association with a
3 control element derived from an OP-1 inducible protein.
- 1 5. The method of any of claims 1-4 wherein said sample further comprises
2 part or all of a Type II serine/threonine kinase receptor protein
3 having binding affinity for OP-1, activin or BMP-4.

- 1 6. A method for producing an OP-1 receptor binding analog, the method
2 comprising the steps of:
- 3 (a) obtaining, by the method of any of claims 1-5, a candidate OP-1
4 binding analog, and
- 5 (b) producing either said candidate analog or a second OP-1 binding
6 analog derived from said candidate and having substantially the
7 same OP-1 receptor-binding domain as said candidate.
- 1 7. The method of producing an OP-1 receptor-binding analog of claim 6
2 wherein said analog produced in step (b) is by recombinant DNA
3 techniques, or by nonbiological peptide synthesis.
- 1 8. A kit for identifying OP-1 or a candidate OP-1 receptor binding analog
2 in a sample, the kit comprising:
- 3 (a) a receptacle adapted to receive a sample and containing a protein
4 selected from the group consisting of:
- 5 (i) a polypeptide chain comprising an amino acid sequence
6 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an
7 OP1-binding analog thereof;
- 8 (ii) a polypeptide chain comprising an amino acid sequence
9 defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an
10 OP1-binding analog thereof;
- 11 (iii) a polypeptide chain comprising an amino acid sequence
12 defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an
13 OP1 binding analog thereof;
- 14 (iv) a polypeptide chain having binding affinity for OP-1 and
15 sharing at least 40% amino acid identity with residues 23-
16 122 of Seq. ID No. 7 (ALK-6),;
- 17 (v) a polypeptide chain having binding affinity for OP-1 and
18 encoded by a nucleic acid obtainable by amplification with
19 one or more primer sequences defined by Seq. ID Nos. 12-15;
20 or
- 21 (vi) a polypeptide chain having binding affinity for OP-1 and
22 encoded by a nucleic acid that hybridizes under stringent
23 conditions with a nucleic acid comprising the sequence
24 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;
25 and
- 26 (b) means for detecting interaction of OP-1 or a candidate OP-1
27 receptor-binding analog with said protein of part (a), said OP-1

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28 or candidate analog comprising part of said sample provided to
29 said receptacle.

1 9. The kit of claim 8 wherein said means in part (b) comprises either
2 (i) means for detecting specific binding interaction of OP-1
3 or said candidate analog with said protein; or
4 (ii) means for detecting induction of an OP-1 mediated cellular
5 response.

1 10. The kit of claim 8 or 9 further comprising a serine/threonine Type II
2 receptor having binding specificity for OP-1, activin or BMP-4.

1 11. An OP-1 receptor-binding analog produced by the method of any of claims
2 1-7 or use of the kit of claims 8-10.

1 12. The analog produced by the method of any of claims 1-8, said analog
2 (i) comprising an amino acid sequence sharing greater than 60%
3 identity with the C-terminal 96 amino acids of the sequence
4 represented by Seq. ID No. 9 (OP-1, residues 335-431), and
5 (ii) being substantially incapable of inducing an OP-1 mediated
6 cellular response.

1 13. The analog of claim 11 or 12 further having binding affinity for a
2 Type II serine/threonine kinase cell surface receptor.

1 14. The analog of claim 13 wherein said Type II receptor also has binding
2 affinity for activin or BMP-4.

1 15. An isolated ligand-receptor complex comprising two molecules
2 interacting as specific binding partners, the first said molecule
3 defining said ligand and comprising at least the C-terminal 96 amino
4 acids of OP1 (residues 335-431 of Seq ID No. 9) or a receptor-binding
5 analog thereof, and the second said molecule defining said receptor and
6 being selected from the group consisting of:

7 (i) a polypeptide chain comprising an amino acid sequence
8 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an
9 OP1-binding analog thereof;

10 (ii) a polypeptide chain comprising an amino acid sequence
11 defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an
12 OP1-binding analog thereof;

13 (iii) a polypeptide chain comprising an amino acid sequence
14 defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an
15 OP1 binding analog thereof;

- 16 (iv) a polypeptide chain having binding affinity for OP-1 and
17 sharing at least 40% amino acid identity with residues 23-
18 122 of Seq. ID No. 7 (ALK-6),;
19 (v) a polypeptide chain having binding affinity for OP-1 and
20 encoded by a nucleic acid obtainable by amplification with
21 one or more primer sequences defined by Seq. ID Nos. 12-15;
22 or
23 (vi) a polypeptide chain having binding affinity for OP-1 and
24 encoded by a nucleic acid that hybridizes under stringent
25 conditions with a nucleic acid comprising the sequence
26 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),.

- 1 16. The complex of claim 15 further comprising part or all of a Type II
2 serine/threonine kinase receptor .
1 17. The complex of claim 16 wherein said Type II receptor also has binding
2 affinity for activin or BMP-4.
1 18. The complex of any of claims 15-17 wherein said first molecule defining
2 said ligand is an OP-1 receptor-binding analog comprises part or all
3 of the proteins selected from the group consisting of 60A, BMP-5, BMP-
4 6, Vgr-1, OP2, OP3 and receptor-binding amino acid sequence variants or
5 xenogenic homologs thereof.
1 19. An isolated binding partner having specific binding affinity for an
2 epitope on a ligand-receptor complex, said complex being characterized
3 as comprising an OP-1 protein or an analog thereof in specific binding
4 interaction with the ligand binding domain of a cell surface receptor
5 defined by Seq. ID No. 3 (ALK-2), 5, or 7, or an OP1-binding analog
6 thereof; said binding partner having substantially no binding affinity
7 for the uncomplexed form of said OP-1 protein or OP-1 protein analog.
1 20. The isolated binding partner of claim 19 wherein said binding partner
2 is further characterized as having substantially no binding affinity
3 for the uncomplexed form of said cell surface receptor protein or said
4 analog thereof.
1 21. The binding partner of claim 19 wherein said binding partner is a
2 monoclonal or polyclonal antibody.
1 22. Use of the OP-1 receptor-binding analog of any claims 11-14 in a method
2 for
3 (i) antagonizing OP-1 binding to a cell surface receptor; or
4 (ii) antagonizing induction of an OP-1 mediated cellular
5 response.

- 1 23. The use according to claim 22 wherein said OP-1 receptor-binding analog
2 comprises an antibody having binding specificity for
- 3 (i) the ligand binding domain of a cell surface receptor defined
4 by Seq. ID Nos. 3, 5, or 7 or an OP-1 binding analog
5 thereof; or
- 6 (ii) the receptor binding domain of OP-1, represented by Seq. ID
7 No. 9, or a receptor-binding analog thereof.

- 1 24. Use of a protein selected from the group consisting of:

- 2 (i) a polypeptide chain comprising an amino acid sequence
3 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an
4 OP1-binding analog thereof;
- 5 (ii) a polypeptide chain comprising an amino acid sequence
6 defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an
7 OP1-binding analog thereof; .
- 8 (iii) a polypeptide chain comprising an amino acid sequence
9 defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an
10 OP1 binding analog thereof;
- 11 (iv) a polypeptide chain having binding affinity for OP-1 and
12 sharing at least 40% amino acid identity with residues 23-
13 122 of Seq. ID No. 7 (ALK-6),;
- 14 (v) a polypeptide chain having binding affinity for OP-1 and
15 encoded by a nucleic acid obtainable by amplification with
16 one or more primer sequences defined by Seq. ID Nos. 12-15;
17 or
- 18 (vi) a polypeptide chain having binding affinity for OP-1 and
19 encoded by a nucleic acid that hybridizes under stringent
20 conditions with a nucleic acid comprising the sequence
21 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;

22 in a method for antagonizing

- 23 (i) OP-1 binding to a cell surface receptor; or
24 (ii) induction of an OP-1 mediated cellular response.

- 1 25. A method for antagonizing activin binding to a cell surface receptor,
2 the method comprising the step of:

- 3 providing a cell expressing a said receptor with a protein having
4 binding specificity for the amino acid sequence defined by
5 residues 16-123 of Seq ID No. 3 or an OP-1 binding sequence
6 variant thereof, said protein sharing at least 60% amino acid

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7 sequence identity with residue 335-431 of the sequence defined by
8 Seq ID No. 9,

9 such that said protein, when provided to said cell, is competent
10 to interact specifically with said receptor, thereby
11 substantially inhibiting activin binding to said receptor.

1 26. A method for antagonizing BMP-4 binding to a cell surface receptor, the
2 method comprising the step of:

3 providing a cell expressing a said receptor with a protein having
4 binding specificity for the ligand binding domain defined by
5 residues 24-152 of Seq ID No. 5 (ALK-3), or residues 23-122 of
6 Seq ID No. 7 (ALK-6), or an OP-1 binding sequence variant
7 thereof, said protein sharing at least 60% amino acid sequence
8 identity with residues 335-431 of the sequence defined by Seq ID
9 No. 9,

10 such that said protein, when provided to said cell, is competent
11 to interact specifically with said receptor, thereby
12 substantially inhibiting BMP-4 binding to said receptor.

1 27. Use of the OP-1 receptor binding analog of claim 12-14 in the method of
2 claim 25 or 26.